acquiescence with regard to the Examiner's rejections, and are made without prejudice to prosecution of any subject matter modified and/or removed by this amendment in a related divisional, continuation and/or continuation-in-part application. Applicants acknowledge the Examiner's comments regarding the Oath/Declaration and submit herewith a corrected Declaration.

Rejection Under 35 U.S.C. § 103

Claims 19-24 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Van Eldik *et al.* (PNAS 81: 6034-38, 1984), Okada *et al.* (U.S. Patent No. 5,320,944) and Shibue *et al.* (U.S. Patent No. 5,240,863). According to the Examiner, Van Eldik *et al.* teaches monoclonal antibodies to S100β having the amino acid sequence of SEQ ID NO: 2 and SEQ ID NO: 3. The Examiner further asserts that the antibodies of Van Eldik *et al.* specifically react with S100β as determined by ELISA analysis. Okada *et al.* allegedly teaches a dual antibody ELISA where antibodies are bound to a magnetic particle carrier. Shibue *et al.* allegedly teaches dual antibody ELISA wherein the immunoreactant measurement is via electrochemilluminescence. The Examiner concludes that it would have been prima facie obvious to the skilled artisan to modify the ELISA (with S100β antibody) of Van Eldik *et al.* with the dual antibody sandwich assay of Okada *et al.* and Shibue at al. using magnetic carrier immobilization and detection via chemiluminescence.

Applicants respectfully traverse this rejection.

Applicants note that the currently claimed invention relates methods for determining the presence of human S-100β polypeptide in a sample comprising the steps of reacting the sample to be analyzed immunologically with a first monoclonal antibody specific for a first peptide having the amino acid sequence of SEQ ID NO:2 or a peptide having the amino acid sequence of SEQ ID NO: 3, wherein said first antibody is coupled to a carrier, and then reacting said sample immunologically with a second monoclonal antibody specific for a second peptide having the amino acid sequence of SEQ ID NO:2 or a peptide having the amino acid sequence of SEQ ID NO: 3, wherein said second peptide is not identical to said first peptide. Consequently, the claimed invention unambiguously requires the use of two distinct antibodies

that are specific for two distinct epitopes of the S100β protein, one being specific for an amino acid sequence of SEQ ID NO: 2 and the other being specific for SEQ ID NO: 3.

As an initial matter, Applicants submit that Van Eldik *et al.* cannot be considered an enabling document with respect to their described antibodies because the antibodies are not deposited according to the Budapest Treaty, and, moreover, Van Eldik *et al.* explicitly states that such antibodies are extremely difficult to obtain. Accordingly, any antibody taught by Van Eldik *et al.* is simply not enabled as to its structure and/or specificity, and, consequently, is similarly not enabled for any immunological assay that relies on the described antibody.

However, even to the extent this reference is considered enabling for the antibodies described therein, the skilled person would not have been able to predict in an obvious manner or with a reasonable expectation of success which portions of S100β would have been important in providing polypeptides and their use in reliable immunoassays that permit sensitive detection of S100β without cross-reactivity to S100.

Van Eldik *et al.* fails to describe even a single immunological subfragment of S100β that is recognized by an S100β-specific antibody, much less two distinct S100β antibodies that are specific for two distinct epitopes of the S100β protein, one being specific for an amino acid sequence of SEQ ID NO: 2 and the other being specific for SEQ ID NO: 3, as required by Applicants' claimed methods.

Furthermore, Van Eldik *et al.* describe the production of a single antibody, not two different antibodies having two different specificities. This is inferred from the passage on page 6035, right column, penultimate paragraph stating that "in all considerations done to date, the two monoclonal antibodies are indistinguishable in their reactivities" (page 6035, right column, lines 53 to 55). By failing to describe two distinct antibodies that are specific for two distinct epitopes of the S100β protein, Van Eldik *et al.* cannot reasonably lead the skilled artisan to Applicants claimed methods.

As for the cited secondary references, Okada *et al.* and Shibue *et al.* are devoid of any disclosure related to antibodies specific for S100β, and, on this basis alone, fail to remedy the deficiencies of Van Eldik *et al.* Okada *et al.* teache magnetic particles obtained by binding an antibody to the coated particles (column 4, lines 33 to 36). Okada *et al.*, however, do not teach the use of any S100β antibody and does not identify any immunological subfragments of

S100β. Shibue *et al.* describe a method of measuring an immunoreactant using electrochemiluminescence. Shibue, however, does not provide any information relating to a dual antibody ELISA, does not teach the use of any S100β antibody, and does not identify any immunological subfragments of S100β.

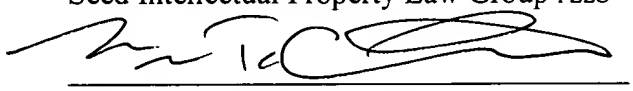
Applicants respectfully submit that the combined disclosure of Van Eldik *et al.*, Okada *et al.*, and Shibue *et al.*, cannot reasonably render obvious to the skilled artisan the currently claimed invention when the combined disclosure of these references simply fails to teach, suggest, or otherwise motivate a skilled artisan to arrive at, Applicants' immunological methods employing two distinct S100β antibodies that are specific for two distinct epitopes of the S100β protein. Reconsideration and withdrawal of this rejection is thus respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**"

All of the claims in the application are believed to be in condition for allowance. The Examiner is invited to contact the undersigned at (206) 622-4900 with any questions, comments and/or suggestions relating to this matter.

Respectfully submitted,

Seed Intellectual Property Law Group PLLC



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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

New claims 25-29 have been added.

25. (New) The method according to claim 19, wherein the monoclonal antibody specific for the amino acid sequence of SEQ ID NO: 2 is specific for amino acid residues 6-38 of SEQ ID NO: 2.

26. (New) The method according to claim 19, wherein the monoclonal antibody specific for the amino acid sequence of SEQ ID NO: 2 is specific for amino acid residues 20-35 of SEQ ID NO: 2.

27. (New) The method according to claim 19, wherein the monoclonal antibody specific for the amino acid sequence of SEQ ID NO: 3 is specific for amino acid residues 5-10 of SEQ ID NO: 3.

28. (New) The method according to claim 19, wherein the monoclonal antibody specific for the amino acid sequence of SEQ ID NO: 2 is specific for amino acid residues 6-38 of SEQ ID NO: 2 and wherein the monoclonal antibody specific for the amino acid sequence of SEQ ID NO: 3 is specific for amino acid residues 5-10 of SEQ ID NO: 3.

29. (New) The method according to claim 19, wherein the monoclonal antibody specific for the amino acid sequence of SEQ ID NO: 2 is specific for amino acid residues 20-35 of SEQ ID NO: 2 and wherein the monoclonal antibody specific for the amino acid sequence of SEQ ID NO: 3 is specific for amino acid residues 5-10 of SEQ ID NO: 3.